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NO EFFECT OF PEGYLATED INTERFERON-ALPHA ON TOTAL HIV-1 DNA LOAD IN HIV-1/HCV COINFECTED PATIENTS

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Running head: pIFN- α in HIV-1/HCV coinfecting patients (39/40 characters and spaces allowed)

Summary: Total HIV-1 DNA was quantified in HIV-1/HCV coinfecting patients receiving pIFN- α treatment. Total HIV-1 DNA remained stable before, during, and after pIFN- α treatment, which questions the benefit of pIFN- α as an immunotherapeutic agent for reducing the HIV-1 reservoir.

ABSTRACT

Pegylated interferon-alpha (pIFN- α) is suggested to lower HIV-1 DNA load in antiretroviral therapy (ART) treated patients. We studied the kinetics of total HIV-1 DNA levels in 40 HIV-1/hepatitis C (HCV) coinfecting patients, treated with pIFN- α for HCV and categorized into three groups according to start of ART: Chronic HIV-1 infection (n=22), acute HIV-1 infection (n=8), no-ART (n=10). Total HIV-1 DNA levels were quantified in 247 PBMC samples and remained stable before, during, and after pIFN- α treatment in all three groups. Our study results question the benefit of pIFN- α as an immunotherapeutic agent for reducing the HIV-1 reservoir.

BACKGROUND

Eradication of human immunodeficiency virus type 1 (HIV-1) infection is not attainable by antiretroviral drugs alone, due to the HIV-1 reservoir formed early during acute infection [1]. Pegylated interferon alpha (pIFN- α), used to treat hepatitis C virus (HCV) infection, represents an interesting candidate to reduce the HIV-1 reservoir due to its variable antiviral and immune stimulating properties against HIV-1 [2, 3]. However, effects of pIFN- α on total HIV-1 DNA levels, a well-validated marker of the HIV-1 reservoir [4], in antiretroviral therapy (ART) receiving, HIV-1 infected patients is not fully understood and there are conflicting results concerning the effects and mechanisms of pIFN- α .

To examine benefits of pIFN- α treatment in reducing total HIV-1 DNA levels, we conducted a study including 40 HIV-1/HCV coinfecting patients from the Swiss HIV Cohort Study (SHCS), and the Zurich Primary HIV Infection Study (ZPHI). Unique to our study, we included patients from three groups: (i) HIV-1 chronic, (ii) HIV-1 acute - both stratified according to time to initiation of ART after HIV-1 infection – and (iii) a no-ART HIV-1 infected group, all with long follow-up times post pIFN- α treatment. We hypothesized that pIFN- α would lead to sustained reduction of the total HIV-1 DNA.

PATIENTS, MATERIALS, AND METHODS

Study Design

This is a retrospective study using prospectively collected clinical information and blood samples obtained within protocols of the ZPHI and SHCS (supplementary information 1) and stored in respective biobanks. Complete inclusion and exclusion criteria can be found in the supplementary information 2. In brief, inclusion criteria for HIV-1 infected, ART treated patients were: (i) HCV-coinfection and a history of pIFN- α /RBV treatment for ≥ 24 weeks; (ii) no history of virological failure; (iii) no history of ART interruption; (iv) on suppressive

combination ART; (v) documented ART-adherence of $\geq 95\%$ [5]. Exclusion criteria were: ≥ 1 blip during ART before start of pIFN- α /RBV. Inclusion criteria for no-ART HIV-1 infected patients were: (i) HCV-coinfection and history of pIFN- α /RBV treatment for ≥ 24 weeks and, (ii) ART-naïve at time of pIFN- α /RBV initiation, during and ≥ 1 year after pIFN- α /RBV treatment.

Patient groups were defined as chronic when ART was started ≥ 6 months after the estimated date of infection (EDI), as acute when ART was started < 6 months after EDI, and as no-ART when patients were not on ART as defined above. Information on pIFN- α dosage and administration can be found in the supplemental information 3.

Quantitation of total HIV-1 DNA

Genomic DNA was isolated from ≥ 2 million cryopreserved PBMCs using DNeasy Blood & Tissue Kits (Qiagen) according to the manufacturer's description except that two elution steps, each with 45 μ l of pre-heated (70°C) AE elution buffer, were applied. Total HIV-1 DNA was quantified in duplicates by qPCR with cycling profile: 95 °C 5 min, 50x (95 °C 15 sec, 60 °C 30 sec) using forward and reverse primers H7 and H1, alongside the probe mf381tq. To measure genomic input, the single copy reference gene CC Chemokine Receptor 5 (CCR5), was quantified using primers mf51 and mf52 with the probe mf73tq (Supplementary Table 1). Quantification was done using an in-house HIV-1 all-in-one Standard (supplemental information 4, supplementary figure 1 A and B).

Quantitation of HIV-1 viral load

Values for HIV-1 RNA copies/mL plasma were obtained from patients' clinical history. These values were measured using Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 assay versions

1 and 2. Detection limits were either 40 or 20 HIV-1 RNA copies/mL plasma for version 1 and 2, respectively.

Cell Counts

CD4+, CD8+, and CD3+ T-cells were quantified by flow cytometry following routine laboratory protocols.

Statistical analysis

Wilcoxon matched-pairs signed rank test were applied to assess changes in total HIV-1 DNA, HIV-1 viral load, and cell counts using GraphPad Prism Version 5.04 (La Jolla, CA).

RESULTS

Patient population and HCV treatment

Forty HIV-1/HCV-coinfected individuals were categorized into three patient groups according to their stage of HIV-1 infection at the time of ART initiation: (i) chronic HIV-1 infection (n=22), (ii) acute HIV-1 infection (n=8), and (iii) no-ART (n=10). Baseline demographics and clinical characteristics are depicted in Table 1.

Total HIV-1 DNA levels remain stable during pIFN- α treatment

We quantified total HIV-1 DNA in 247 PBMC samples with a mean number of time points (range) per patient of 6.6 (2-12) in the chronic, 5.6 (2-10) in the acute and 5.7 (3-9) in the no-ART groups. The average follow-up time after pIFN- α treatment is depicted in Table 1.

We analysed total HIV-1 DNA levels in PBMCs obtained prior to pIFN- α treatment (Figure 1). Values were grouped according to time of pIFN- α treatment and median values were calculated. We found that total HIV-1 DNA levels (median HIV-1 DNA copies/ 10^6 genomic equivalents [range]) were 0.15 log₁₀ higher in the chronic (1652 [67.4-9807]) versus the acute group (1156 [50.2-2516.7], $p=0.07$), as well as 0.74 log₁₀ higher than in the no-ART group (298.1 [6.9-3635], $p=0.06$).

We evaluated the effect of pIFN- α /RBV treatment on total HIV-1 DNA. We observed no decrease in total HIV-1 DNA levels during administration of pIFN- α /RBV in any of the three patient groups (Figure 1). Some patients across all groups (chronic $n=8$, acute $n=4$, no-ART $n=1$) had even moderate increases in total HIV-1 DNA levels during pIFN- α treatment ($p>0.05$). After pIFN- α treatment, total HIV-1 DNA returned to the same levels as before pIFN- α treatment in the acute and chronic groups. In the no-ART group, total HIV-1 DNA levels after pIFN- α treatment were higher ($p=0.02$) than total HIV-1 DNA levels before pIFN- α treatment (individual total HIV-1 DNA profiles provided in supplementary figures 2A, 2B, 2C). As interferon is known to cause general lymphopenia, we calculated the total HIV-1 DNA levels normalised to CD4⁺ T-cell counts, but observed no change in the total HIV-1 DNA kinetics. Of note, four patients (C6, C19, C20, and A4) underwent repeated pIFN- α treatments due to non-response to previous HCV treatment. In all four patients, no sustained decrease in total HIV-1 DNA levels was detected (supplementary figures 2A and 2B).

pIFN- α decreases the HIV-1 viral load in the no-ART group

As IFN- α is known to have anti-viral effects against HIV-1, we studied effects of pIFN- α HIV-1 on viral load in the no-ART group. The mean viral load decreased by 0.8 log₁₀ ($p=0.004$) during treatment as compared to pre-treatment levels. After pIFN- α treatment cessation, viral load returned to pre-treatment levels (Figure 1D). All patients in the chronic and acute groups maintained undetectable viral loads (<20-40 HIV-1 RNA copies/mL plasma) during pIFN- α treatment (supplementary figure 3).

pIFN- α -induced lymphopenia observed in T-cell subsets

As expected, during pIFN- α treatment we observed a significant drop in mean values (cell count/ μ L of blood) of CD4+ ($p<0.0001$), CD8+ ($p<0.0001$), and CD3+ ($p<0.0001$) T-cells and in absolute lymphocyte counts in comparison to pre-pIFN- α levels. After treatment stop, all lymphocyte subsets returned to pre-treatment levels (supplementary figure 4).

DISCUSSION

In 40 well-characterized HIV-1/HCV-coinfected patients, we longitudinally assessed effects of pIFN- α treatment on total HIV-1 DNA levels in PBMCs, a surrogate marker for the HIV-1 reservoir [4]. We observed that total HIV-1 DNA levels remained stable during and after pIFN- α in comparison to pre-treatment levels, also in patients who underwent repeated pIFN- α treatments.

To dissect potential effects of pIFN- α with regard to the timing of ART initiation, we analysed three different HIV-1/HCV coinfected patient groups: (i) HIV-1 infected patients treated with ART during chronic HIV-1 infection; (ii) HIV-1 infected patients treated with ART during acute HIV-1 infection, and (iii) untreated HIV-1 infected patients. Baseline total HIV-1 DNA levels in the acute group were 0.15 log₁₀ lower compared to patients treated during the

chronic stage of infection. This observation is in line with several studies, showing that patients treated in the early stage of HIV-1-infection have substantially lower total HIV-1 DNA levels compared to individuals treated during chronic phase [6]. The low total HIV-1 DNA levels observed in the no-ART group are most likely due to selection of patients controlling HIV-1 well in absence of ART, which is associated with low total HIV-DNA levels [7]. Six of the ten patients in this group showed viral loads of <5,000 HIV-1 RNA copies/mL plasma before pIFN- α treatment, with one being an elite controller (Figure 1D) [7]. Viral load was assessed in the no-ART group before, during, and after pIFN- α treatment and a reduction of 0.8 log₁₀ observed. This finding is in line with the results of several clinical trials reporting an approximately 0.5-1 log₁₀ decrease in viral load when pIFN- α is administered to HIV-1-infected persons in absence of ART [8].

With regard to effects of pIFN- α administration on the total HIV-1 DNA levels, our findings differ from previous studies. Sun *et al.* (2014) reported a moderate reduction of CD4+ T-cell-associated total and integrated HIV-1 DNA in 12 HIV-1/HCV-coinfected individuals treated with pIFN- α for a median of 51 weeks [9]. In their study, reductions of HIV-1 DNA occurred mainly in patients without treatment-associated lymphopenia, suggesting that the decline in HIV-1 DNA levels did not result simply from lymphocellular toxicity of pIFN- α treatment. In our study, all patients exhibited pIFN- α associated lymphopenia and no reduction in HIV-1 DNA levels from PBMC was observed. A recent study [10] found results more in line with ours as authors did not detect any change in total HIV-1 DNA levels in 10 patients receiving a short-term pIFN- α treatment of 28 days.

A possible explanation for the absence of a HIV-1 DNA decrease is that our assay measures total HIV-1 DNA, however, this is not only a measure of replication competent viruses [11]. The study from Morón-López *et al.* [10] where the replication competent reservoir was measured by viral outgrowth assay (VOA) in patients receiving pIFN- α /RBV showed no change in the number of infectious units per million CD4+ T-cells (IUPM) from

patients on ART. The absence of an HIV-1 DNA decrease is unlikely resulting from insufficient pIFN- α treatment as (i) all our patients exhibited lymphopenia, (ii) the no-ART group showed an RNA decline of 0.8 log₁₀, and (iii) 90% had a sustained virological response of the HCV infection.

The strength of this work is that, to our knowledge, our study is to date the largest one investigating the effects of pIFN- α on total HIV-1 DNA levels in people on suppressive antiretroviral therapy. The longitudinal nature is unprecedented with patients being followed up for as long as 112 months post pIFN- α . Limitations are that due to the retrospective nature of our study, we investigated only effects of pIFN- α on total HIV-1 DNA in cryopreserved patient PBMCs. As we did not investigate cells from other biological compartments, we may have missed tissue-specific pIFN- α effects. We also did not differentiate between integrated and non-integrated proviral HIV-1 DNA. However, it has been shown that after one year of ART almost no linear unintegrated HIV-1 DNA exists anymore [12] and our ART-treated patients were virologically suppressed for ≥ 1 year before of pIFN- α administration. Moreover, we did not use the VOA, which is suggested as the gold standard for HIV-1 latency, although it fails to detect a considerable fraction of inducible latently infected cells [13]. Finally, our study population did not include patients who received pIFN- α administration close to the time of HIV-1 acquisition. Thus, a potential beneficial pIFN- α effect on the establishment of the HIV-1 reservoir, which is formed early after HIV-1 infection [14] cannot be ruled out. The only study exploring pIFN- α together with antiretroviral treatment in 12 acutely HIV-1 infected patients, however, found a total HIV-1 DNA decay that was similar to that found in acutely infected ART treated patients alone [12, 15]. Thus, pIFN- α would probably need to be administered much earlier, which is hardly achievable in clinical practice.

In summary, our longitudinal study in different well-characterized patient groups did not reveal any substantial effect of pIFN- α on the HIV-1 reservoir as measured by a total HIV-1 DNA qPCR assay in PBMCs. Thus, our study does not support a sustainable effect of pIFN- α as an immunotherapeutic intervention in patients who have initiated ART during acute or chronic HIV-1 infection or who are off ART to reduce the HIV-1 reservoir.

FOOT NOTE PAGE

Conflicts of Interests and Source of Funding

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AUTHORS CONTRIBUTION STATEMENT

HFG, KJM and DLB conceptualized, designed and supervised the study. Data acquisition was done by VPS, DLB, VV, AUS, YLK, RDK, MS, AR, KD, MH, KJM, HFG. Data analysis was done by VPS, AUS, RDK, HFG and KJM. A first draft of the manuscript was written by

VPS, DLB, RDK, KJM and HFG. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript and approved the final manuscript.

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Table 1. SHCS Patient Characteristics at baseline (pre IFN- α /Ribavirin treatment). Significant p values are italicised.

Data	chronic group (n=22)	acute group (n=8)	no-ART group (n=10)	chronic versus acute (p=)
Age (years) at time of pIFN-α treatment, mean (range)	45 (37-55)	38 (27-45)	42 (32-53)	<i>0.005</i>
Gender (%)				
Male	21 (95.5)	8 (100)	7 (70)	>0.9
Female	1 (4.5)	0 (0)	3 (30)	>0.9
Ethnicity (%)				
Caucasian	22 (100)	8 (100)	10 (100)	n.a.
Risk Group^a (%)				
MSM	5 (22.7)	7 (87.5)	4 (40)	<i>0.003</i>
HET	1 (4.5)	1 (12.5)	1 (10)	0.46
IDU	11 (50)	0	2 (20)	<i>0.01</i>
IDU or HET	3 (13.6)	0	3 (30)	0.54
IDU or MSM	2 (9.1)	0	0	>0.9
HIV Subtype (%)				

B	22 (100)	7 (87.5)	8	0.27
Non B	0	1 (12.5)	1	0.27
Unknown	0	0	1	
Time under Suppressive ART^b, months (range)	42.4 (7-110)	39.4 (4-98)	n.a. ^d	0.9
HCV Genotype				
1	9	3	1	>0.9
2	0	0	1	>0.9
3	9	1	6	0.21
4	2	2	0	0.28
Unknown	2	2	2	n.a.
HCV Treatment^c				
pIFN- α	1	0	0	>0.9
pIFN- α + RBV	21	7	10	0.47
IFN- α + RBV	0	1	0	0.27
Treatment Duration (weeks), mean (range)	48.1 (24-68)	40.5 (24-48)	38.7 (20-51)	0.04
SVR 12 or 24^e with IFN-α (%)				
Yes	19 (86.4)	7 (87.5)	9 (90)	>0.9

No	1 (4.5)	1 (12.5)	1 (10)	0.46
Unknown	2 (9.1)	0	0	>0.9
Follow up (months)^f, mean (range)	46.6 (3-112)	13.3 (0-34)	43.9 (3-99)	0.003

^aMSM= men who have sex with men, HET= heterosexual, IDU= intravenous drug use.

^bSuppressive ART defined as treatment controlling HIV-1 RNA <50 copies/mL plasma

^cpIFN- α =Pegylated Interferon alpha, RBV= Ribavirin, IFN- α = Interferon alpha

^dn.a. = Not applicable as were not on antiretroviral treatment at the time of Interferon administration

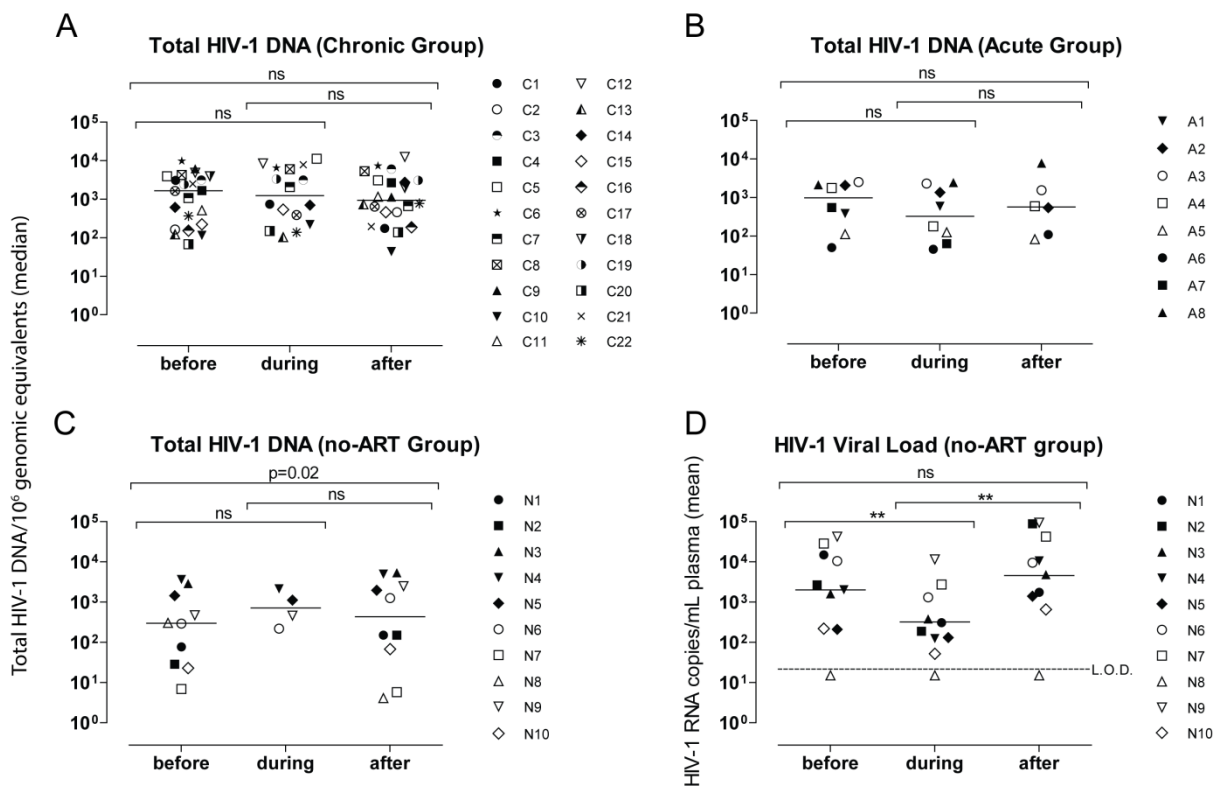
^eSustained Virological Response against HCV

^fAfter stop of Interferon-alpha treatment

Figure 1: Total HIV-1 DNA levels remain stable before, during, and after pIFN- α treatment periods in all three groups (chronic, acute, and no-ART) of HIV-1/HCV coinfecting patients with the HIV-1 viral load decreasing in the no-ART group.

Total HIV-1 DNA values are calculated to 10^6 genomic equivalents (CCR5). Treatment period is displayed on the x axis, and median total HIV-1 DNA load on the y axis. Statistical significance is displayed as $^*(p \leq 0.05)$, or ns (no significance). Each symbol and corresponding number (for example C1, A1, and N1) refers to an individual patient in the chronic, acute, or no-ART group. (A) Patients who started antiretroviral therapy (ART) during the chronic stage of HIV-1 infection and later went on to receive pIFN- α for a HCV infection. (B) Patients who started ART during the acute stage of HIV-1 infection and later received pIFN- α for a HCV infection. (C) Patients who received no ART at the time of pIFN- α administration. (D) Pegylated interferon alpha decreases the HIV-1 viral load in the no-ART group. HIV-1 viral load (RNA copies/mL plasma) is plotted as mean values for before, during, and after pIFN- α treatment periods. The samples below the limit of detection (L.O.D.) appear below the dashed line. The L.O.D. is below 40 and 20 HIV-1 RNA copies/mL plasma for Roche Cobas Taqman HIV-1 assay version 1 and 2, respectively. Statistical significance is displayed as ** ($p \leq 0.01$), or ns (no significance). Individual patients are depicted by a symbol and corresponding ID.

Figure 1.



pegylated interferon- α treatment